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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,757	12/08/2000	David Mack	A-69795/DJB/JJD	2797

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 02/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,757	MACK ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 32-43 in Paper No. 14 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 44-47 have been canceled.

3. Claims 32-43 are pending and under examination.

Specification

4. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code, which are impermissible and require deletion, see for example page 14, lines 25-26, page 10, line 6.

The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding incorporation by reference.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 32-43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well-established utility.

Claims 32-43 are drawn to a method for diagnosing colorectal cancer, wherein said method comprises determining the expression of the nucleic acid molecule of SEQ ID NO: 1 or a gene at least 75% identical to SEQ ID NO:1 in colorectal tissue of a first individual and comparing said expression of the gene in the first sample to expression in a second sample, wherein said comparison is used to diagnose colorectal cancer.

In the specification, Applicants disclose their discovery that the level of expression of the nucleic acid of SEQ ID NO: 1 in a colorectal cancer specimen is higher than the level of expression in a normal, non-tumor specimen. In light of their discovery, Applicants assert that determination of the level of expression of the nucleic acid molecule of SEQ ID NO: 1 in a particular specimen acquired from an individual and comparison of this level of expression with the level of expression in a second tissue can be used as a means for diagnosing colorectal cancer in the individual.

While the specification does disclose the expression levels in colorectal cancers and some normal tissues it is not clear that there is a discernable amount of expression in some of the normal tissue versus the cancerous tissues. In addition, it cannot be ascertained whether the normal specimen was acquired from the same individual from

which the tumor specimen was acquired or from a different individual. Furthermore, it is unclear whether one tumor specimen or multiple tumor specimens were analyzed or whether one normal specimen or multiple normal specimens were analyzed for comparison.

On page 30, the specification defines the term "differential expression" (lines 13-32). According to the disclosure, "The degree to which expression differs need only be large enough to quantify" (page 30, lines 24 and 25). Certainly one skilled in the art would not accept the assertion that *any* quantifiable difference in the level of expression of a gene is indicative of the presence of colorectal cancer in an individual. Then, somewhat incongruously, the specification teaches, "preferably the change in expression (i.e., upregulation or downregulation) is at least about 50%, more preferably at least about 100%, more preferably at about 150%, more preferably, at least about 200%, with from 300 to at least 1000% being especially preferred" (page 30, lines 29-31). However, it is noted that comparing some of the tissues in Figures 3B and 3C with Figure 3A do not result in a difference of expression, for example B2 S 2527 in Figure 3A with Prostate or CEP samples in Figure 3C and 3B respectively. Thus, it would seem that a determination of the levels of expression of SEQ ID NO:1 in just any tissue and comparison thereof would not be useful for diagnosis of colorectal cancer, because the change in expression (i.e., up-regulation) is less than 50% and the specification teaches that a difference in expression of at least about 50% is preferable. Certainly, one skilled in the art would not accept the assertion that a difference of less than 50% in the level of expression of a gene would be indicative of the presence of colorectal

cancer in an individual and thus would not accept the assertion that any of the nucleic acid molecules SEQ ID NO:1 or a molecule of 75% identity to SEQ ID NO:1 could be used in practicing the claimed method with a reasonable expectation of success.

In summary, for the reason set forth above, the invention is not supported by a credible asserted utility and most certainly, the use or utility of the claimed method is not well established. Consequently, the claimed invention fails to meet the utility requirement under 35 USC § 101.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 32-43 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. Claims 32-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for diagnosing colorectal cancer by determining the expression of a gene that is 75% identical to SEQ ID NO:1 or SEQ ID NO:1. However, the teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims. Accordingly, one skilled in the art cannot practice the invention with a reasonable expectation of success without first performing extensive and undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

As stated in the 35 USC § 101 rejection above, the specification does not teach a clear distinction between the expression of SEQ ID NO:1 in colorectal cancer tissue versus many normal tissues. The specification does not exemplify the method using a gene that is 75% identical to SEQ ID NO:1. Moreover, there is insufficient guidance in the specification that would enable one skilled in the art to practice the claimed invention with a reasonable expectation of success without first having to perform extensive and undue experimentation. In fact, apart from reciting that the invention provides a method for diagnosing colorectal cancer (page 2, lines 20-21, for example), there is very little disclosure that is considered pertinent to the enablement of the

claimed method. Therefore, clearly the specification provides insufficient guidance to enable the skilled artisan to practice the claimed invention with a reasonable expectation of success. In particular, it is noted that the specification fails to disclose the threshold value of the difference in the levels of expression of SEQ ID NO:1 or a nucleic acid molecule 75% identical to SEQ ID NO:1 that can be used to discriminate the individual that has primary or metastatic colorectal cancer from the individual that is disease-free. Furthermore, based only upon the disclosure that the nucleic acid of SEQ ID NO: 1 is expressed at a higher level in colorectal cancer than in normal, non-tumor tissue, one skilled in the art would not accept the assertion that the claimed method can be used successfully with a nucleic acid molecule that is SEQ ID NO:1 or 75% identical to SEQ ID NO:1, because the art is highly unpredictable and therefore clinical applicability of the claimed method can only be determined empirically. There is no factual evidence of record that would reasonably convince one skilled in the art that the invention can be used to effectively diagnose any type of colorectal cancer.

The molecular diagnosis of cancer is a highly unpredictable art. For example, Rae, et al (*International Journal of Cancer* **88**: 726-732, 2000) teach a method for determining the differential expression of genes in renal cell carcinoma (RCC) (abstract). Rae, et al disclose that a total of sixteen tumor and sixteen adjacent normal tissue samples were collected at the same time from patients. Rae, et al also disclose that the tumor tissue was histologically confirmed to be clear-cell RCC and the tumors were staged by a conventional system (page 726, column 2). Rae, et al teach that the use of differential display PCR, some genes were identified that are expressed at higher

levels in the tumor specimens than in the normal specimens while other genes were expressed at lower levels in the tumor specimens (abstract). In any case, Rae, et al, disclose, "only those cDNAs clearly up- or down-regulated in duplicate paired RCC and normal kidney samples (Fig. 1) from 4 different patients were considered to be definitively differentially expressed" (page 728, column 1). Rae, et al teach that results were considered only when the cDNAs were successfully re-amplified and only when no expression was detected in the paired sample (page 728, column 2). Notably, Rae, et al had planned to use as a positive control primers that amplify a cDNA encoding DD96, a gene previously shown by Kocher, et al to be up-regulated in RCC (page 728, column 2). However, Rae, et al found in contrast to the results reported by Kocher, et al, no *consistent* up- or down-regulation of *DD96* was evident when using either RT-PCR or Northern analysis. Rae, et al, therefore, conclude, "we do not believe that *DD96* up-regulation is highly associated with RCC, particularly in early progression, and does not warrant extensive further investigation in the context of this disease" (page 731, column 2). Incidentally, there is no disclosure that suggests that Applicants' methods were as thorough as the teachings of Rae, et al would suggest is necessary and there is also no factual evidence that the results disclosed in the specification are reproducible.

In view of the teachings of Rae, et al, it is evident that the instant disclosure is not enabling, because in the absence of substantial factual evidence that the invention can be used to diagnose colorectal cancer in a patient, one of skill in the art cannot predict whether the invention can be used and would therefore not be able to practice the

invention with a reasonable expectation of success without first performing extensive and undue experimentation.

In comparing Figures 3A-C it is entirely possible that the alteration in the level of expression of the nucleic acid molecule of SEQ ID NO: 1, is the result of some epigenetic event(s) that occur late in tumor cell development. If so, there is little reason to expect the invention to be a valuable diagnostic marker, because one skilled in the art appreciates the fact that only early diagnosis is efficacious in treating the disease. Also, the specification discloses nothing of the biologic role of the protein encoded by the nucleic acid molecule of SEQ ID NO: 1; therefore, it is unclear whether the protein even has a role in the etiology or pathology of colorectal cancer.

Ward (*Developmental Oncology* **21**: 91-106, 1985) teaches, not all markers can be reliably used in primary diagnosis; rather, some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease (see abstract). Thus, while it is clear that some types of colorectal cancer cells have an altered level of expression of the nucleic acid molecule of SEQ ID NO: 1, this data does not guarantee that the detection of the relative level of over-expression will result in a definitive diagnosis of colorectal cancer.

It is well known in the art that the detection of some tumor markers has proven to be ineffective in enabling an accurate diagnosis of cancer in a subject. Ward (cited supra) teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable (see abstract). Even CA-125, one of the more reliably used biomarkers

known in the art, is not always effective for rendering a diagnosis of ovarian cancer (see US 5,356,817 A; column 2, line 47 to column 3, line 2).

Finally, even if the detection of an altered level of expression of the nucleic acid molecule of SEQ ID NO: 1 were found to clinically useful, there are insufficient guidelines for use of the resultant data acquired by the detection such a marker in the specification to enable one skilled in the art to use the invention to diagnose an individual with cancer. Tockman et al (*Cancer Research* **52**: 2711s-2718s, 1992) teach considerations necessary in bringing a cancer biomarker (intermediate endpoint marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to risk assessment, diagnosis, and/or prognosis of any type of cancer. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of

disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate endpoint marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, these must be validated against acknowledged disease end points; and, the marker predictive value must be confirmed in prospective population trials (page 2716, column 2).

Also, in practical use, contaminating normal cells in the isolated specimen may obscure any difference in the level of expression in cancer cells relative to normal cells. This would tend to severely limit the specificity and the sensitivity of the claimed method. Consequently, the skilled artisan would be required to exquisitely dissect the tumor specimen, insuring complete removal of non-tumor tissue to be certain of accurately measuring the level of expression of the gene in the tumor. The specification, however, provides no guidance with regard to this issue.

In view of the above, it is clear that one skilled in the art would not accept the assertion that the invention can be used effectively to diagnose colorectal cancer of any type in the absence of exemplification that is commensurate in scope with the claims. Again, the specification does not enable the use of the claimed method using SEQ ID NO:1 or a gene that is 75% identical to SEQ ID NO:1 to render a diagnosis of colorectal cancer.

The specification does not enable a method wherein the samples are from just any tissue type. One skill in the art would readily conclude that colorectal tissue needs to be one of the tissues examined. It has not been shown that a metastatic sample from

colorectal tissue can be used to diagnose or that tissue from just any source can be used. In addition, the specification has not demonstrated that the expression of SEQ ID NO:1 is constant or similar in normal samples from several individuals. It is not clear from the data in Figures 3A-C If there is a general correlation between normal individuals for expression of SEQ ID NO:1 and if this can be used to diagnose using just any "normal sample".

Moreover, the asserted utility of the invention is entirely unproven and therefore reasonably considered incredible. As stated above, one skilled in the art cannot predict whether the invention can be used effectively. Actually, in view of the fact that alterations in the level of expression of the nucleic acid molecule of SEQ ID NO: 1 may occur late in the development of a tumor, one might doubt that the invention can be used effectively. Therefore, one skilled in the art cannot use the invention with a reasonable expectation of success without first performing extensive and undue experimentation.

10. Claims 32-40 and 42-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to method of diagnosing colorectal cancer with detection of expression of a gene at least 75% identical to SEQ ID NO:1. The specification only discloses SEQ ID NO:1 can be used for diagnosis. There is no other nucleic acid

disclosed for the intended use for diagnosis of colon cancer. It is clear that the written description is insufficient to reasonably convey to one skilled in the art that Applicants' had possession of the invention at the time the application was filed. Evidence of conception of an invention alone is not reasonable inference that Applicants' had possession of the invention at the time the application was filed. In the absence of exemplification and sufficient guidance, there is no factual evidence of record that would suggest that a reduction to practice had occurred at the time the application was filed. For this reason, the specification fails to meet the written description requirement of 35 USC § 112, first paragraph. This is a written description rejection.

11. Claims 32-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a "gene" of 75% identical to SEQ ID NO:1 or a gene of SEQ ID NO:1. According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as "the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons)." From the teachings of the specification, however, the nucleic acid sequences introducing antigens or marker elements appear limited to the specific coding regions, and do not include expression control elements that fall under the definition of a gene.

For this reason, the specification fails to meet the written description requirement of 35 USC § 112, first paragraph. This is a written description rejection.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 32-43 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-43 are rejected because claim 32 does not recite a positive correlation step that clearly relates back to the preamble of the claim. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending claim 32 to recite, for example, the phrase "whereby colorectal cancer is diagnosed" at the end of the last line of the claim can obviate this rejection.

Claims 32-43 are vague and indefinite because claim 32 recites the phase "first sample" and second sample" because it is not clear where the samples are from or if they are the same tissue type or if they are suspected of having cancer or are the same individual.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879